TICK-BORNE ENCEPHALITIS (TBE) VACCINE

Susan Hills, MBBS, MTH
Medical Epidemiologist
Arboviral Diseases Branch
Centers for Disease Control and Prevention

February 23, 2022

Work Group activities since last meeting and recommendations for consideration and vote

- Work Group considered ACIP members' feedback
  - Recommended and Shared Clinical Decision-Making categories for travel vaccines
  - Providing best clarity as vaccine more likely given by general healthcare than travel medicine providers

- TBE vaccine recommendations: request for three votes
  - 1st vote: Recommendation for laboratorians
  - 2nd and 3rd votes: Recommendations for persons who travel abroad
    1. "Recommended" component
    2. "Shared clinical decision-making" component

Guidance for categories of recommendations

- Recommended category:
  - Vaccine should be recommended if there is any group of people who should receive the vaccine (i.e., the benefits of receiving the vaccine clearly outweigh the risks*)

- Shared clinical decision-making category:
  - No group for whom the vaccine should be recommended but some individuals might reasonably choose vaccination and some providers might reasonably wish to recommend it for some travelers

    OR
  - There are any groups of people where the benefits of receiving the vaccine might not outweigh the risks* or there is uncertainty

*Risk-benefit consideration should weigh factors such as the likelihood of exposure (based on location, season, time, and activities), risk of disease and its potential severity, vaccine's efficacy, and possibility of serious vaccine-associated adverse events

Note on shared clinical decision-making category

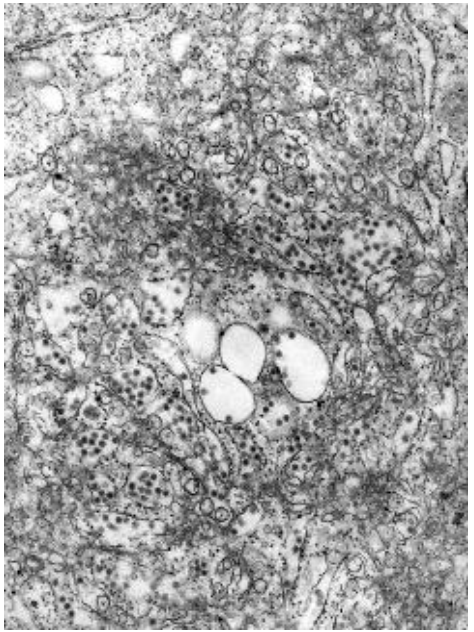
- Travel vaccines often require consultation with a healthcare provider to identify which, if any, are indicated, based on a traveler's age; travel plans including destinations, duration, and activities; and other risk factors
  - Not shared clinical decision-making

Brief review of TBE and TBE vaccine

TBE virus

- Flavivirus related to Powassan virus

- Three main subtypes differ in
  - Geographic distribution
  - Severity of disease they cause



TBE virus photo credit: Alamy images

TBE virus transmission

- Transmitted by *Ixodes* species ticks

- Infections usually acquired in wooded areas during
  - Recreational activities (e.g., camping, hiking, fishing, hunting)
  - Outdoor occupations (e.g., forestry service, farming)

https://www.ecdc.europa.eu/en/tick-borne-encephalitis;©ECDC/Photo by Guy Hendrickx

TBE in endemic areas

- Focally endemic in parts of Europe and Asia
- ~5,000–10,000 cases reported annually
- Incidence variable
  - Country-to-country
  - Within countries
  - Year-to-year
- Seasonal risk from April through November

Source: Dobler et al, Wien Med Wochenschr 2012

Disease risk and outcome

- Very low numbers of cases among U.S. persons
  - 11 cases in U.S. civilian travelers, 2001–2020
  - 9 cases in military personnel, 2006–2020

- Potentially high fatality and sequelae rates with neuroinvasive disease

Photo credits: Getty images

TBE vaccine

- TBE vaccine (TICOVAC) approved by FDA in 2021 for use in persons aged ≥1 year
- Current formulation available internationally for >20 years
- >75 million doses administered
- Marketed in ~30 countries, primarily in Europe

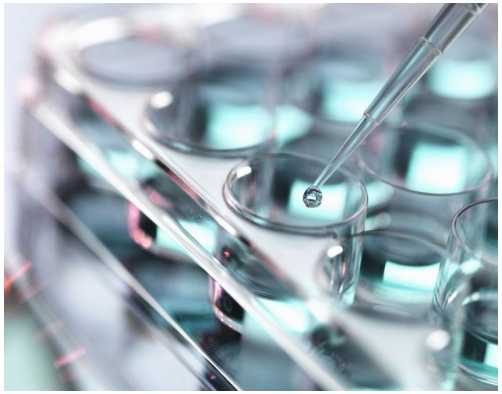
GRADE assessment results

- Immunogenicity
  - Seropositivity rates high after primary series and after booster dose
  - Likely but unconfirmed protection against non-European TBE virus subtypes
- Safety
  - Vaccine-related serious adverse events rarely reported

Laboratory workers

Key considerations for development of recommendations for laboratory workers working with TBE virus

- Transmission has occurred through aerosol route
  - Percutaneous or mucosal route possible
- >46 laboratory-acquired infections globally
- <10 U.S. laboratories work with TBE virus
- Vaccination will reduce risk of potentially severe disease
- Implementation feasible through existing occupational health programs



Balance of consequences from Evidence to Recommendations framework

- Desirable consequences clearly outweigh undesirable consequences in most settings

Proposed recommendation

- TBE vaccination is recommended for laboratory workers with a potential for exposure to TBE virus.

Persons who travel abroad

Key factors for development of recommendations for persons who travel abroad: Is there a group who should receive the vaccine?

- Overall risk of disease
- Potential severity of disease
- Patterns of disease transmission
- Risk factors for disease among U.S. travelers
- Tick-related factors
- Vaccination recommendations in endemic countries
- Vaccine-related factors

Disease risk for U.S. civilian travelers

- Very rare disease with 11 cases diagnosed during past 20 years
- Risk for all U.S. travelers to TBE endemic countries is <1 TBE case per 30 million trips
- Risk among group of travelers visiting specific risk areas, traveling during transmission season, and undertaking activities with risk of tick exposure
  - ~1 TBE case per 2 million trips (range: 0.1–5 cases per million trips)

Potential severity of neuroinvasive disease

- Most persons require hospitalization
  - No antiviral treatment
- Sequelae rates of 10% to 50%
  - Can include permanent physical disabilities or cognitive impairment
- Case fatality rates of 1% to 20%

Patterns and distribution of disease

- Seasonal risk from April through November
- Large outbreaks do not occur
- Some uncertainty in defining risk in specific locations within endemic areas
  - Transmission variable year to year
  - Risk areas can be very focal
  - Accurate data often unavailable

Risk factors for infection among U.S. civilian travelers (N=11)

- Common factors
  - Tick exposure in 100% (8 of 8 with itinerary information)
  - Travel during TBE virus transmission season

- No apparent association with
  - Duration of travel
  - Specific activities
  - Basic demographics
  - Specific travel locations

Tick-related factors

- Humans must enter tick habitats and come in contact with ticks to be at risk

- Travelers do not pose risk for TBE virus establishment in United States

National vaccine recommendations in endemic countries

- One country with universal recommendation
- Some countries with recommendations for populations in specific areas
- Some countries only for persons at highest risk (e.g., outdoor occupations)
- Some countries have no vaccination policy

Vaccine-related factors

- Very good immunogenicity and safety profile
  - Possibility of serious adverse events
- For two TBE virus subtypes, likely but unproven effectiveness
  - Siberian and Far Eastern subtypes occur in eastern part of endemic area and cause more severe disease
- Cost
  - Vaccine paid for out of pocket by most travelers
  - Opportunity costs if purchase TBE vaccine vs. other measures for travel

Work Group conclusions: TBE vaccination recommendation

- Risk for travelers to TBE endemic areas during the transmission season who undertake an activity with risk of tick exposure is very low
  - < 1 TBE case diagnosed per million travelers
- Likely is a smaller group at higher risk
  - All U.S. traveler cases reported activities that put them at risk of tick exposure
  - Travelers with more extensive tick exposure → higher likelihood of infection
- TBE can be severe with risk of sequelae and death
- Safe and effective vaccine

Proposed recommendation

- TBE vaccine is recommended for persons who are moving abroad or traveling to a TBE-endemic area and will have extensive exposure to ticks based on their planned outdoor activities and itinerary.

Is there an additional group for whom shared clinical-decision making is appropriate?

- Any groups of people with uncertainty in the risk-benefit assessment

  OR

- Some individuals might choose vaccination or some providers might recommend it for some travelers

Key factors for development of shared clinical decision-making recommendation

- U.S. traveler TBE cases and extent of exposure to ticks
- Higher risk of poorer medical outcome among some persons
- Variability in perception and tolerance of risk

U.S. traveler TBE cases and extent of exposure to ticks

- Some might not have had extensive exposure to ticks
  - Difficult to assess based on amount of itinerary information available

- To protect all travelers going to TBE endemic locations who might have tick exposure, need to give large number of doses to prevent one case
  - >1 million travelers need to be vaccinated to prevent 1 TBE case

Higher risk of poorer medical outcome among some persons with TBE

- Older persons consistently shown to have poorer outcome[1]

1. Schuler et al, Euro Surveill 2014; Lindquist, Lancet 2008

Personal perception and tolerance of risk

- Survey on vaccination decisions for disease similar to TBE and vaccine similar to TBE vaccine[1]
  - 32% somewhat or very *likely* to be vaccinated and 43% somewhat or very *unlikely* to be vaccinated[2]
  - 1 in 1 million risk of a severe disease was key factor in decision-making for both groups, indicating different perceptions and tolerance of risk

1. Hills SL et al. Perceptions among the U.S. population of value of Japanese encephalitis (JE) vaccination for travel to JE-endemic countries. Vaccine 2020
2. 25% unsure

Work Group conclusions: additional shared clinical decision-making component of TBE vaccine recommendations

- Some travelers might be exposed to ticks but will not have extensive exposure, and several factors might be considered in risk-benefit assessment
  - Very low risk of disease; heterogeneity based on activities and itinerary
  - Some persons might have risk factors for poorer medical outcome
  - Differences in personal perception and tolerance of risk for a severe disease like encephalitis

Proposed recommendation

TBE vaccine might be considered for persons traveling or moving to a TBE-endemic area who might engage in outdoor activities in areas ticks are likely to be found. The decision to vaccinate should be based on an assessment of their planned activities and itinerary, risk factors for a poorer medical outcome, and personal perception and tolerance of risk.

Proposed recommendations

Proposed TBE vaccine recommendations

Laboratory workers

- TBE vaccination is recommended for laboratory workers with a potential for exposure to TBE virus.

Persons who travel abroad

- TBE vaccine is recommended for persons who are moving abroad or traveling to a TBE-endemic area and will have extensive exposure to ticks based on their planned outdoor activities and itinerary.
- (*In addition*) TBE vaccine might be considered for persons traveling or moving to a TBE-endemic area who might engage in outdoor activities in areas ticks are likely to be found. The decision to vaccinate should be based on an assessment of their planned activities and itinerary, risk factors for a poorer medical outcome, and personal perception and tolerance of risk.

TBE Vaccine Work Group members and participants

ACIP

Katherine Poehling (Chair)

Wilbur Chen

CDC Lead

Susan Hills, DVBD

Ex Officio

Rodolfo (Rudy) Alarcon, NIH

Ihid Carneiro Leao, FDA

ACIP liaisons

David Shlim, ISTM

Mark Sawyer, AAP

Technical advisors

Alan Barrett, Univ Texas Galveston

Lin Chen, Mount Auburn Hosp

Anthony Marfin, PATH

Bruce McClenathan, DOD

Kayvon Modjarrad, DOD

Technical advisors (cont'd)

Steven Schofield, CATMAT

Bryan Schumacher, DOD

Mary Wilson, Univ Calif SFO

CDC participants

Grace Appiah, DGMQ

Doug Campos-Outcalt, Consultant

Susan Chu, GID

Caitlin Cossaboom, DHCPP

CDC participants (cont'd)

Stacey Martin, DVBD

Michael McNeil, DHQP

Rebecca Morgan, Consultant

Erin Staples, DVBD

Steve Waterman, DVBD

ACIP Secretariat

Jessica MacNeil, NCIRD

Melinda Wharton, NCIRD